J of Nuclear Medicine Technology, first published online June 25, 2015 as doi:10.2967/jnmt.115.159400

Title: Nuclear Myocardial Perfusion Imaging versus Stress Echocardiography in the Preoperative Evaluation of Patients for Kidney Transplantation

Short running title: Preoperative testing in renal transplant

Janice N. Thai, MD[1]; Aiden Abidov, MD, PhD[2]; Tun Jie, MD[3]; Elizabeth A. Krupinski, PhD[1]; Phillip H. Kuo, MD, PhD[1]

[1]Department of Medical Imaging

University of Arizona Medical Center

1501 N. Campbell Avenue

PO Box 245067

Tucson AZ 85724

[2]Department of Medicine

Division of Cardiology

University of Arizona Medical Center

[3]Department of Surgery

Division of Abdominal Transplantation

University of Arizona Medical Center

Corresponding author:

Phillip H. Kuo, MD, PhD

Professor, Department of Medical Imaging

Section Chief, Nuclear Medicine

Address:

University of Arizona Medical Center

1501 N. Campbell Ave

PO Box 245067

Tucson AZ 85724-5067

Telephone: (520) 626-1957

Facsimile: (520) 626-9074

Email: pkuo@radiology.arizona.edu

Reprint requests directed to Phillip H. Kuo.

Disclosures:

PHK is a consultant for GE Healthcare and received grant support from Astellas.

AA received grant support from the National Institutes of Health (NIH), Astellas, GLOBAL and is a consultant for GLOBAL. He is on the advisory board of Advance Cardiac Imaging Consortium (ACIC) and Cardinal Health.

Abstract:

The goal of this study was to evaluate the diagnostic accuracy, cost-effectiveness and appropriate use of SPECT myocardial perfusion imaging (SMPI) versus stress echocardiography (SE) in the preoperative evaluation of patients for kidney transplantation.

Methods:

A single-institution, retrospective study was performed. SMPI was performed with regadenoson and stress echocardiography predominantly with dobutamine. Findings on subsequent coronary angiography were correlated. Utilizing reimbursements from the Center for Medicare Services (CMS), a cost analysis for SMPI versus stress echocardiography was modeled.

Results:

113 patients underwent imaging (53 SMPI and 60 stress echocardiography). 100% of SMPI studies were diagnostic compared to only 80% (48/60) in the stress echocardiography group, and this result was statistically significant ($X^2 = 7.96$, $p < 0.01$). The most common reason for a non-diagnostic test was not reaching target heart rate. In the SMPI group, 15% (8/53) had ischemia on imaging and all had subsequent coronary angiography which confirmed obstructive coronary lesions. One patient with negative SMPI had subsequent angiogram that was negative. In the stress echocardiography group, 5% (3/60) had ischemia on imaging and two had subsequent angiography, which were negative. Three of 12 patients with non-diagnostic exams underwent further testing. One patient had a follow-up positive SMPI but no subsequent coronary angiography. The other two patients underwent coronary angiography that were negative. Of the 45 negative stress echocardiography, six (13%) had angiography with positive result for obstructive coronary artery disease in 3/6. For modeling of cost analysis, CMS rates of $1,173

and $1,521 were utilized for SMPI and stress echocardiography respectively. The model assumes that all non-diagnostic imaging would be referred for further stress testing (i.e. non-diagnostic stress echocardiography would be referred for SMPI). This model estimates that initial non-invasive testing with stress echocardiography versus SMPI results in 50% greater cost.

Conclusion:

For preoperative evaluation of kidney transplantation, SMPI is more often diagnostic than stress echocardiography. A cost model estimates that initial non-invasive diagnostic testing with stress echocardiography would result in approximately 50% greater cost compared to SMPI. Our data also suggests that SMPI has greater diagnostic accuracy than stress echocardiography. Therefore, this single institution experience supports SMPI as the more appropriate test.

Key words: Myocardial perfusion imaging, kidney transplant evaluation, cardiac risk stratification, cost analysis

Introduction:

Kidney transplantation candidates represent a unique patient population with often higher than average medical complexity and comorbidity burden. Cardiovascular disease, specifically coronary artery disease (CAD), is a leading cause of morbidity and mortality for this population before and after transplantation. Estimates of the cumulative incidence of myocardial infarction (MI) based on Medicare billing claims have ranged from 8.7% to 16.7% by 3 years after kidney transplant listing, and from 4.7% to 11.1% after kidney transplantation between 6 and 36 months (*1,2*). The surgery for kidney transplantation is typically considered an "elevated-risk" procedure and cardiac risk stratification is warranted to identify patients who are at increased risk for perioperative cardiac events due in part to pathophysiology of end-stage renal disease. Cardiac

evaluation practices vary amongst institutions and clinicians. The Clinical Practice Guidelines (CPG) published in 2012 by the American Heart Association (AHA) and the American College of Cardiology (ACC) aimed to provide the framework in which to conduct perioperative cardiac assessment, cardiovascular risk prediction and treatment algorithm in the most recent version of the AHA/ACC scientific statement "Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates" (*3*).

The value of cardiac screening for myocardial ischemia is to identify those likely to benefit from revascularization or optimization of medical management. Even though there is no strong evidence for or against cardiac screening of asymptomatic patients, the current consensus justify screening on the basis of the presence of multiple CAD risk factors, regardless of stratification by functional status as assessed by estimated metabolic equivalents of task (METs) (*3*). Relevant risk factors include advanced age, diabetes mellitus, prior cardiovascular disease, more than 1 year on dialysis, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension and dyslipidemia (Class IIb; Level of Evidence C).

Methods of screening vary from exercise or pharmacological stress nuclear myocardial perfusion imaging, exercise or pharmacological stress echocardiography, and direct cardiac catheterization with coronary angiography without preceding non-invasive testing. Non-invasive stress testing is reported as the most common first approach to cardiac evaluation (*4*). Prospective randomized controlled trials (RCT) are not available on optimal screening strategies for the presence of clinically or physiologically significant CAD to guide the approach and choice of a perioperative cardiac imaging modality. For patients who cannot exercise, there is currently no RCT comparing different pharmacological stress testing methods. In light of insufficient data, local expertise in performing stress testing, patient-specific factors and specific

clinical questions should be considered in decisions about the most appropriate diagnostic test. Both myocardial perfusion nuclear stress with single-photon-emission computed tomography (SPECT) and stress echocardiography can reliably detect stress-induced myocardial ischemia, myocardial viability and CAD (*3*). The established sensitivity and specificity for detecting angiographically defined CAD (≥ 50% luminal diameter reduction) are roughly comparable between the two established modalities. Sensitivity for SPECT vs stress echocardiography has been shown in various studies to be 85 to 90% vs 75 to 80%, and specificity 65 to 70% vs 80 to 85%, respectively (*5-12*). More importantly, in a recent meta-analysis, echocardiographic and nuclear perfusion imaging are equivalent for the diagnosis of inducible ischemia with a negative predictive value of 98% for adverse cardiovascular outcomes over the next 3 years (*13*). Therefore the invariably high prognostic value of a negative result validates their essential role in cardiac risk stratification as an initial screening modality for CAD.

The paucity of literature directly comparing various methodologies for cardiac stress testing in the preoperative evaluation for kidney transplantation population is the motivation for our investigation. At our institution, a regionally accredited abdominal transplantation center, all patients undergoing preoperative evaluation for kidney transplantation are routinely imaged for CAD with either SPECT myocardial perfusion imaging (SMPI) or stress echocardiography. We have similarly high expertise of the professional and technical staff in performing and interpreting both modalities. This multidisciplinary investigation was undertaken as a quality initiative study, with the participation of team members from medical imaging, cardiology and abdominal transplantation. We set out to perform a direct comparison by systematically evaluating the diagnostic performance, economics, safety and appropriate use of SMPI versus

stress echocardiography in the kidney transplant population. In addition, a hypothetical cost per patient model was created to reflect the cost-effectiveness of one modality compared to the other.

Materials and Methods:

Study design and patient population

A single-institution, retrospective study was performed. The institutional review board approved this study and the requirement to obtain informed consent was waived. Data were collected on all consecutive patients with end-stage renal disease who were evaluated for kidney transplantation from 2012-2014. All patients have been entered into a prospectively maintained database after initial consultation with a transplant surgeon or transplant nephrologist. A total of 198 patients were analyzed. Data included age, gender, cardiac risk factors, medical comorbidities, and cardiac imaging results with any reported adverse events. Cardiac risk factors included advanced age, prior history of CAD, diabetes mellitus, hypertension, dyslipidemia, peripheral vascular disease, cerebrovascular disease, family history of early CAD death and duration of dialysis were documented. A complete chart review was performed on each patient via the electronic health record. Physician documentation of the history and physical, hospitalization record, clinic follow-up visit, and any cardiac adverse event documented were obtained.

Image acquisition and data analysis

All SMPI studies were performed with pharmacologic agent regadenoson. Stress echocardiography studies were predominantly performed with pharmacologic agent dobutamine, and a small subset used treadmill exercise. Image acquisition and interpretation methods are in accordance with standard rest/stress protocols. Positive findings of ischemia were correlated with

findings on subsequent coronary angiography, as the gold standard of reference. A diagnosis of significant coronary artery stenosis or obstructive lesions were defined as ≥ 50% luminal diameter narrowing. Two physicians blindly reviewed the results of coronary angiography for concordance with results of SMPI and/or stress echocardiography. Utilizing reimbursement rates from the Center for Medicare Services (CMS) (*14*), a cost analysis for SMPI versus stress echocardiography was modeled.

Statistical analysis

Analysis was performed using StatView statistical software. Results are presented as mean ± SD. Group comparisons for nominal variables were performed using the chi-square comparison test. Group comparisons for scale variables were performed using the one way ANOVA test. All tests were performed using two-tailed analysis. A p-value of 0.05 or less was considered to be statistically significant.

Results:

Patient demographics

A total of 113 patients underwent non-invasive cardiac imaging to evaluate for CAD, with 53 SMPI and 60 stress echocardiography (51 dobutamine and 9 treadmill exercise). A relatively homogenous group was defined, with a study population that did not differ substantially in clinical characteristics. Both groups had similar demographics and cardiac risk factors. For the SMPI cohort, 35 were male, 18 female; mean age was 55±10 (range 35-77). For the stress echocardiography group, 30 were male, 30 female; mean age was 54±10 (range 22-70). No patient in either group had active cardiac symptoms. Cardiac risk factors for both groups were comparable with regard to the following: all patients had at least 2 cardiac risk factors, with

diabetes being the most common. Specifically, with regard to prior history of CAD, the SMPI group had 9 patients, and the stress echocardiography group had 6 patients. These patients had documented history of myocardial infarction (MI), angiographic evidence of coronary stenosis, with or without percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). With regard to dialysis dependency, 32 (60%) patients in the SMPI group were on dialysis at the time of kidney transplant evaluation, while 42 (70%) patients in the stress echocardiography group had dialysis-dependent renal failure. Five patients had undergone kidney transplant and five patients were deceased from non-cardiac related death, at the time of data analysis.

Comparison between SMPI vs Stress echocardiography

100% of SMPI studies were diagnostic compared to only 80% (48/60 in the stress echocardiography group, and this result was statistically significant ($X^2 = 7.96$, $p < 0.01$). Commensurately, 20% (12/60) of the stress echocardiography exams were not diagnostic. The most common reason for a non-diagnostic test was not reaching target heart rate (85% maximal age predicted heart rate) in 12 patients.

In the SMPI group, 15% (8/53) had ischemia on imaging and all 8 patients had subsequent coronary angiography which confirmed obstructive coronary lesions. One patient with negative SMPI had subsequent angiogram, which was negative. In the stress echocardiography group, 5% (3/60) had ischemia on imaging and 2 out of 3 patients had subsequent angiography which were negative. Three of 12 patients with non-diagnostic exams underwent further testing. One patient had a follow-up positive SMPI but no subsequent coronary angiography. The other two patients underwent coronary angiography that were negative. Of the 45 negative stress

echocardiography, 6 (13%) had angiography with positive result for obstructive coronary artery disease in 3/6 (Figure 1).

For modeling of cost analysis, CMS hospital charges for 2014 of $1,173 and $1,521 were utilized for SMPI and stress echocardiography respectively (*14*). The model assumes that all non-diagnostic imaging would be referred for further stress testing (i.e. non-diagnostic stress echocardiography would be referred for SMPI). Inputting the data from our institution, the model estimates that initial non-invasive testing with stress echocardiography versus SMPI results in 50% greater cost (Figure 2).

Complications of procedure

Although not statistically significant, we found 6% (4/60) patients who underwent stress echocardiography had a significant transient adverse effect, with 2 necessitating premature termination of the procedure. One case was reported for each of these events: atrial fibrillation, dizziness, shortness of breath, loss of consciousness (non-responsiveness which prompted cardiopulmonary resuscitation) and hypertensive urgency with severe headache. Two of these patients had a non-diagnostic test. There were no procedure-related complications in the SMPI group.

Discussion:

In this complex, high-risk population, these results support that SMPI with regadenoson is more often diagnostic and more cost-effective than stress echocardiography. Patients undergoing preoperative evaluation for kidney transplantation routinely undergo cardiac stress imaging as part of their preoperative work-up for risk stratification. Commonly, non-invasive stress testing is used first-line followed by coronary angiography, if indicated. Infrequently, invasive coronary

angiography was sought directly without prior non-invasive testing. Due to the lack of RCT data comparing different modalities to support an optimal testing approach to preoperative cardiac evaluation, at present this decision making process is left to the discretion of the referring physician and thus subject to "physician's preference". Ultimately, results of these tests would guide the decision with regard to optimal medical therapy or coronary revascularization in cases of inducible ischemia in the presence of physiologically significant coronary stenosis.

Although myocardial perfusion nuclear imaging and stress echocardiography are both validated methodologies as initial testing modalities for CAD, each technique has its utility, advantages and limitations. Practical considerations, such as resource availability and utilization, clinical and technical expertise, and cost constraints, must also be taken into account when deciding on the best diagnostic approach. This study presented comparative data from our institutional experience with both modalities in order to guide further testing. A statistically significant difference was found between SMPI and stress echocardiography in the diagnostic rate (100% vs 80%). While not statistically significant, SMPI had 100% diagnostic accuracy while stress echocardiography was associated with false positive and false negative results. Significant adverse event rate was also higher in the stress echocardiography group, when compared to none in the SMPI group. The cost-effectiveness of SMPI vs stress echocardiography was further evaluated with a hypothetical cost model, which estimates that initial non-invasive testing with stress echocardiography versus SMPI results in 50% greater cost. Limitations of this study included small sample size. Also single institution experience may not be generalizable due to differences in local expertise, technical staff and equipment. Patient demographics were similar; however the stress echocardiography group did have more women than men compared

to the SMPI group. An additional limitation is the lack of long-term follow-up and data on clinical outcome.

Conclusions:

Our single institution experience showed that, for the preoperative evaluation of kidney transplantation, myocardial perfusion nuclear stress with single-photon-emission computed tomography (SMPI) is more frequently diagnostic as compared to stress echocardiography and therefore can be modeled to be the more cost-effective initial non-invasive testing for obstructive coronary artery disease. Given that our data also shows a trend towards greater accuracy of SMPI over stress echocardiography, SMPI does not sacrifice accuracy for cost-effectiveness.

Acknowledgement:

The authors thank Amy M. Brewer-Burton for help with the cost benefit analysis.

Disclosures:

PHK is a consultant for GE Healthcare and received grant support from Astellas.

AA received grant support from the National Institutes of Health (NIH), Astellas, GLOBAL and is a consultant for GLOBAL. He is on the advisory board of Advance Cardiac Imaging Consortium (ACIC) and Cardinal Health.

References:

1. Lentine KL, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. J Am Soc Nephrol. 2005;16:496-506.

2. Kasiske BL, Maclean JR, Snyder JJ. Acute myocardial infarction and kidney transplantation. J Am Soc Nephrol. 2006;17:900-7.

3. Lentine KL, Costa SP, Weir MR, et al. Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates: A Scientific Statement From the American Heart Association and the American College of Cardiology Foundation. Circulation 2012;126:617-663

4. Danovitch GM, Hariharan S, Pirsch JD, et al. Management of the waiting list for cadaveric kidney transplants: report of a survey and recommendations by the Clinical Practice Guidelines Committee of the American Society of Transplantation. J Am Soc Nephrol. 2002;13:528-35

5. Bax JJ, Wijns W, Cornel JH, Visser FC, et al. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left

ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data. J Am Coll Cardiol 1997;30:1451-60

6. Maddahi J. Myocardial perfusion imaging for the detection and evaluation of coronary artery disease. In: Marcus ML, Schelbert HR, Skorton DJ, Wolf GL, et al., editors. Cardiac imaging principles and practice. 2nd ed. Philadelphia:WB Saunders; 1996

7. Frans J, Wackers HT. SPECT detection of coronary artery disease. In: Dlisizian V, Narula J, Braunwald E, editors. Atlas of Nuclear Cardiology. Philadelphia: Current Medicine inc;2006. Pp35-66

8. Das MK, Pellikka PA, Mahoney DW, et al. Assessment of cardiac risk before nonvascular surgery: dobutamine stress echocardiography in 530 patients. J Am Coll Cardiol. 2000;35:1647-53.

9. Norgan PB, Panomitros GE, Nelson AC, et al. Low utility of dobutamine stress echocardiograms in the preoperative evaluation of patients scheduled for noncardiac surgery. Anesth Analg. 2002;95:512-6.

10. Brown KA, Rowen M. Extent of jeopardized viable myocardium determined by myocardial perfusion imaging best predicts perioperative cardiac events in patients undergoing noncardiac surgery. J Am Coll Cardiol. 1993;21:325-30.

11. Stratmann HG, Younis LT, Wittry MD, et al. Dipyridamole technetium-99m sestamibi myocardial tomography in patients evaluated for elective vascular surgery: Prognostic value for perioperative and late cardiac events. Am Heart J. 1996;131:923-9.

12. Shafritz R, Ciocca RG, Gosin JS, et al. The utility of dobutamine echocardiography in preoperative evaluation for elective aortic surgery. Am J Surg. 1997;174:121-5.

13. Metz LD, Beattie M, Hom R, et al. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol. 2007;49(2):227-237.

14. American Medical Association. Medicare RBRVS: Physician's Guide. Chicago, IL: American Medical Association; 2014.

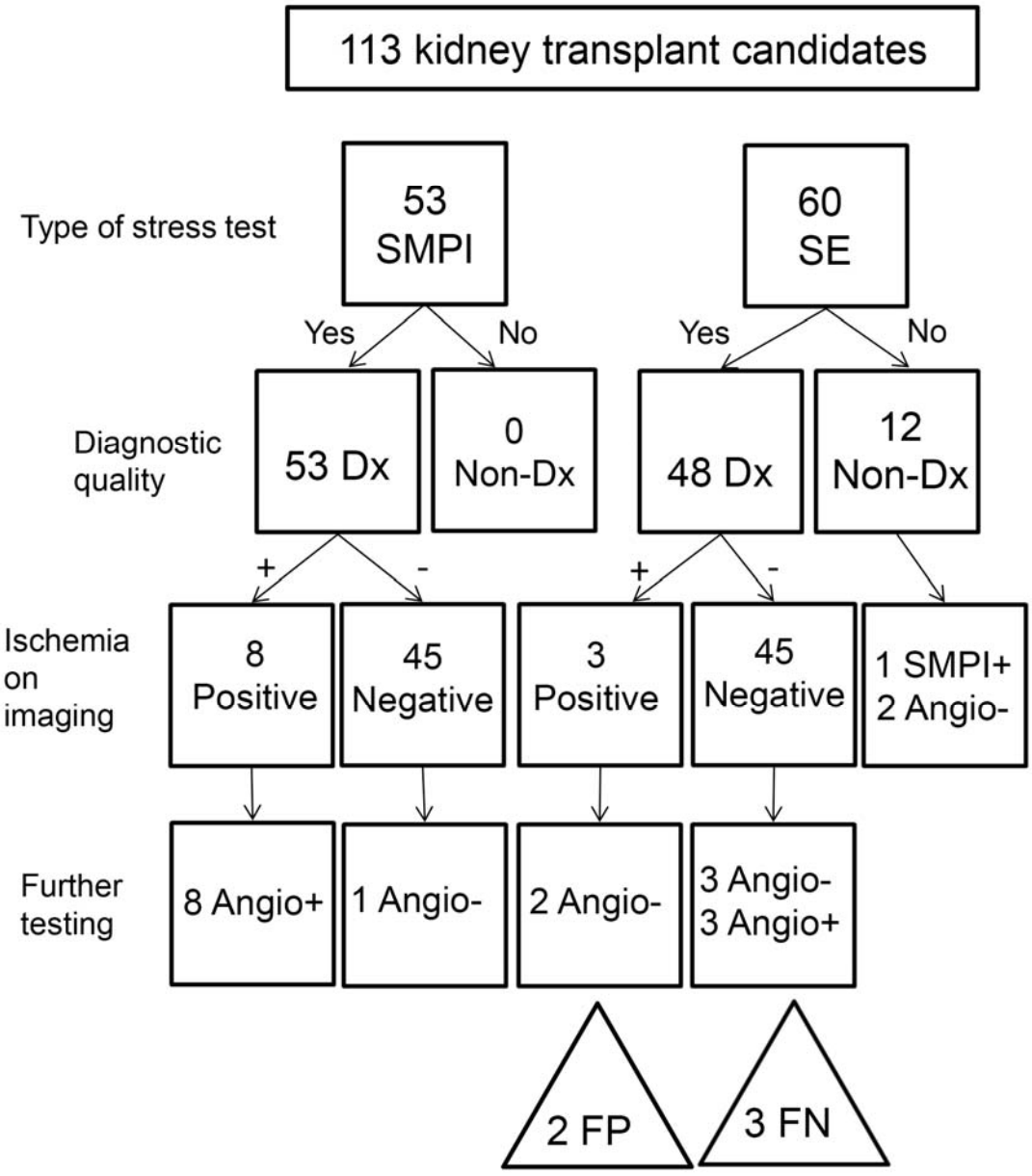

Figure 1: Flow chart of testing for cardiac risk stratification showing the breakdown of patients according first to SMPI versus SE and then by diagnostic quality and further testing

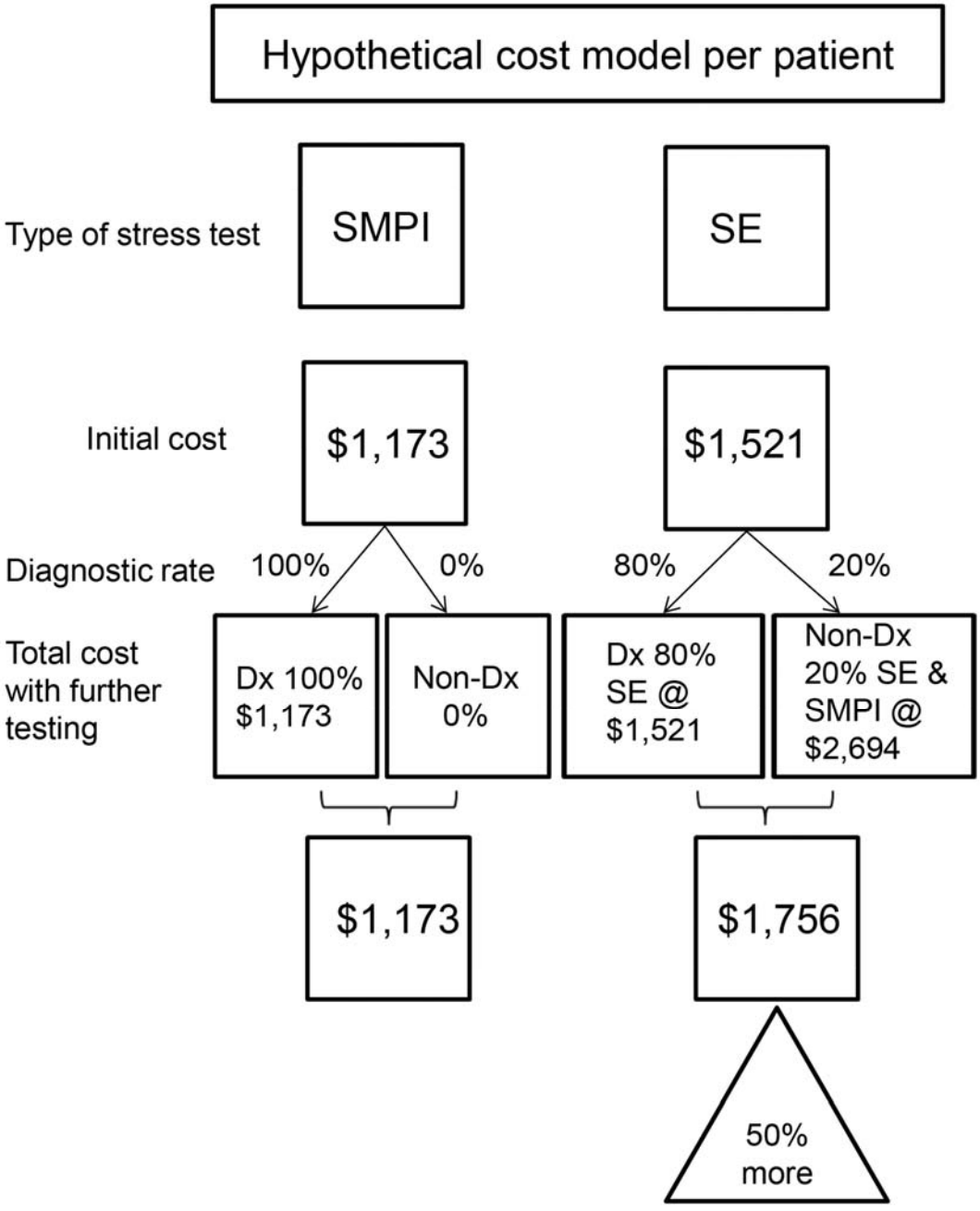

Figure 2: Hypothetical cost model per patient based on CMS hospital charges